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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/347,496	Jiangchun Xu
Examiner	**Art Unit**
Jehanne Souaya	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 26, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-64, 79, 82, and 85-87* is/are pending in the application.

4a) Of the above, claim(s) *1-64* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *79, 82, and 85-87* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Currently, claims 1-64, 79, 82, 85, and newly added claims 86-87 pending in the instant application. Claims 80, 81, 83, and 84 have been canceled, and claims 1-64 have been withdrawn from consideration as being directed to non elected inventions. All the amendments, declarations and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dantzig et al (US Patent 5,710,018; 1/20/1998) in view of Reeves et al (US Patent 6,312,891) and Ahern, H.

("Biochemical, Reagent Kits Offer Scientist Good Return on Investment" from www.the-scientist.library.upen.edu; 1995, pages 1-5).

The claim is drawn to a diagnostic kit comprising at least one oligonucleotide that hybridizes under moderately stringent conditions to a polynucleotide sequence comprising SEQ ID NO 21 and a reporter group for use in a polymerase chain reaction or hybridization assay. It is noted that the specification does not define an upper length limitation for the term oligonucleotide. Dantzig teaches a nucleic acid sequence of 2499 nucleotides that codes for a mammalian influx peptide transporter (see SEQ ID NO 2). SEQ ID NO 21 of the presently claimed invention is identical to nucleotides 1574 to 1918 of SEQ ID NO 2 taught by Dantzig except for a mismatch at nucleotides 1 and 3, and an insertion of an "n" at position 257 of SEQ ID NO 21. It is noted that SEQ ID NO 2 taught by Dantzig would not hybridize to SEQ ID NO 21 of the presently claimed invention under moderately stringent conditions, but that the complement of SEQ ID NO 2 taught by Dantzig would. Dantzig specifically teaches that it would be useful to generate probes that are specific to the conserved extracellular region of the influx peptide transporter (see col. 8, lines 43-45). It is noted that the nucleotides coding for the extracellular portion correspond to nucleotides 1 to 2337 of SEQ ID NO 2 (col 8, lines 26-30) and that a probe comprising this region, which the ordinary artisan would have been motivated to construct based on the teachings of Dantzig, would hybridize to SEQ ID NO 21 under moderately stringent conditions. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed a probe

(oligonucleotide of the presently claimed invention) that would be able to hybridize under moderately stringent conditions to SEQ ID NO 21 of the presently claimed invention as Dantzig teaches that it would be useful to construct a probe specific to the conserved extracellular region of the influx peptide transporter for the purpose of identifying proteins related to the influx peptide transporter. Although Dantzig does not specifically teach constructing a probe for the purposes of hybridizing to SEQ ID NO 21 of the presently claimed invention, the ability to hybridize to SEQ ID NO 21 under moderately stringent conditions is a property of the probe taught by Dantzig. Although Dantzig does not teach a kit comprising an oligonucleotide that hybridizes to SEQ ID NO 21 under moderately stringent conditions and a reporter group for use in a polymerase chain reaction or hybridization assay, it would have further been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the probe taught by Dantzig in kit format as Ahern teaches that researchers are buying premade kits because they are convenient and they save time (see p. 4, second paragraph). Therefore, the ordinary artisan would have been motivated to package the probe taught by Dantzig in kit format for the purposes of having a premade kit ready to use for identifying proteins related to the influx peptide transporter, as Dantzig teaches that such a probe would be useful and Ahern teaches that packaging reagents in kit format is convenient and saves time. Although Dantzig and Ahern do not teach a kit comprising a reporter group for use in a hybridization assay, Reeves teaches the use of labels (or reporter groups) to detect hybridization between a probe and a target, as well as a kit comprising a labeled probe. Reeves specifically teaches that probes can be labeled with a

fluorophore, biotin, a radioisotope, or other tag molecules and the hybridization between the probe and its target can be detected (see col. 4, lines 5-15), and that a kit of the invention of Reeves includes fluorescently labeled oligonucleotide DNA probe (see col. 5, lines 9-14). Therefore, it would have further been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a reporter group (label) as taught by Reeves in the kit of Dantzig and Ahern for the purposes of detecting hybridization between the probe taught by Dantzig and a target.

Applicant is reminded that the use for a kit carries no patentable weight.

Response to Arguments

The response traverses the rejection. The response traverses that nowhere in the cited references is there a discussion of colon cancer or expression levels of the sequence in normal or tumor tissues of any kind, and that therefore, it would not have been obvious to the skilled artisan that this sequence could be used to detect or monitor colon cancer. The response further asserts that the amendment to claim 85, which recites a "kit for use in detection of colon cancer" is unobvious over the cited references. These arguments have been thoroughly reviewed but were found unpersuasive because the "use for" a kit carries no patentable weight. Applicants arguments are analogous to the intended use for a product. The components of the kit remain fully functional regardless of the intended use. Intended used does not impart patentable weight to a product. See MPEP 2111.03:

> Intended use recitations and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the

> claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459, (CCPA 1963).

The intended use which is recited in the preamble of the claim lacks a functional relationship to the kit because the intended use does not physically or chemically affect the chemical nature of the components of the kit, and furthermore, the components of the kit can still be used by the skilled artisan for other purposes (as a whole or individually). Therefore, the kit is unpatentable over the prior art because the components function equally effectively regardless of the intended use, and accordingly no functional relationship exists between the intended use in the preamble of the claims and the kit components.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or

provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claim 85 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 09/922,217 in view of Reeves et al (US Patent 6,312,891) and Ahern, H. ("Biochemical, Reagent Kits Offer Scientist Good Return on Investment" from www.the-scientist.library.upen.edu; 1995, pages 1-5).

The claim is drawn to a diagnostic kit comprising at least one oligonucleotide that hybridizes under moderately stringent conditions to a polynucleotide sequence comprising SEQ ID NO 21 and a reporter group for use in a polymerase chain reaction or hybridization assay. Claim 15 of the '217 application recites a diagnostic kit comprising at least one oligonucleotide that hybridizes to a sequence recited in SEQ ID NO 21 under moderately stringent conditions. It is noted that the recitation of "comprising" in claim 85 of the instant application and "recited in" in claim 15 of the '217 application both encompass the sequence of SEQ ID NO 21. Although claim 15 of the '217 application does note recite a reporter group for use in a polymerase chain

reaction or hybridization assay, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a reporter group in the kit of claim 15 for the purpose of detecting hybridization between the claimed oligonucleotide and SEQ ID NO 21, as exemplified by the teaching of Reeves et al. Reeves teaches the use of labels (or reporter groups) to detect hybridization between a probe and a target, as well as a kit comprising a labeled probe. Reeves specifically teaches that probes can be labeled with a fluorophore, biotin, a radioisotope, or other tag molecules and the hybridization between the probe and its target can be detected (see col. 4, lines 5-15), and that a kit of the invention of Reeves includes fluorescently labeled oligonucleotide DNA probe (see col. 5, lines 9-14). Further, Ahern teaches that researchers are buying premade kits because they are convenient and they save time (see p. 4, second paragraph). Therefore, the ordinary artisan would have been motivated to improve the kit of claim 15 of the '217 application to include a reporter group for the purpose of providing premade reagents in kit format that would be useful for a researcher as Ahern teaches that such would be convenient and would save time.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

The response does not traverse the rejection. The rejection is made FINAL.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 79, 82, 85, and newly added claims 86-87 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The following rejection is maintained with respect to claims 79, 84, and 85, and newly applied to new claims 86 and 87.

Nature of the Invention

The claims are broadly drawn to a method for determining the presence of colon cancer in a patient by detecting, in any biological sample from a patient, hybridization between an oligonucleotide that hybridizes to a polynucleotide sequence (in a biological sample) comprising SEQ ID NO 21, under moderately stringent conditions, and comparing the amount of

oligonucleotide that hybridizes to the polynucleotide with a predetermined cut off value, wherein an increase in the amount of oligonucleotide that hybridizes to the polynucleotide as compared to the predetermined cut off value indicates the presence of cancer in a patient. It should be noted that detecting hybridization between an oligonucleotide that hybridizes to a polynucleotide comprising SEQ ID NO 21, encompasses detecting mutants, homologs, and variants of SEQ ID NO 21. The claims are also drawn to monitoring the progression of colon cancer in a patient by obtaining a biological sample from a patient at different points in time and comparing the amount of oligonucleotide that hybridizes to the polynucleotide in a sample taken at a first point in time with the amount of oligonucleotide that hybridizes to the polynucleotide in a sample taken at subsequent points in time, wherein an increase in the amount of oligonucleotide that hybridizes to the polynucleotide from a sample taken at a subsequent point in time as compared to the first biological sample taken indicates progression of colon cancer and a decrease indicates remission of the colon cancer. Newly added claims 86 and 87 are drawn to determining the presence or absence of colon cancer or the progression of colon cancer in a patient using PCR primers specific for a polynucleotide comprising SEQ ID NO 21 to amplify an expressed product, repeating, and comparing the amount of product to a predetermined cut off value and therefrom determining the presence of colon cancer in a patient. With regard to claim 87, the claim further stipulates that an increase or decrease in amount of product in the second step indicates progression or remission, respectively, of colon cancer.

Amount of Direction and Guidance

The specification teaches using PCR based subtraction of a pool of three colon tumors with a pool of normal colon, spleen, brain, liver, kidney, lung, and other tissues to construct a cDNA library(p. 50) wherein rare transcripts that are overexpressed may be recoverable. The specification teaches that mRNA expression levels were determined using micro array technology and that one hundred and forty nine clones showed two or more fold overexpression in the colon tumor group as compared to the normal tissue group (p. 52). The specification further teaches that SEQ ID NO 21, which has homology to LI cadherin, showed over expression in about half of colon tumors tested and low level overexpression in three out of six normal colon tissues (p. 53, lines 8-10). The specification, however, does not provide any guidance as to how one of skill in the art would distinguish between 'overexpression' and 'low level overexpression'.

Presence and Absence of Working Examples

With regard to claims 79, 82, and 85-87, the specification provides no working examples of detecting colon cancer in a patient by detecting overexpression or an increase in amount, as compared to a predetermined cut off value, of SEQ ID NO 21, in a hybridization assay under moderately stringent conditions or in an RT-PCR assay. Such a method encompasses determining that a patient has colon cancer by detecting an overexpression of mutants, homologs, and variants of SEQ ID NO 21, whereas the specification has provided no teaching that mutants, homologs, and variants of SEQ ID NO 21 are overexpressed in colon tumor tissue, or in any biological sample from a patient with colon cancer. The specification does not provide any

teaching or working examples of detecting the progression of colon cancer in a patient. The specification does not teach whether expression of SEQ ID NO 21, or mutants, variants, or homologs of SEQ ID NO 21 increases or decreases with the progression of colon cancer. With regard to newly added claims 86 and 87, the claims are directed to using primers specific for a polynucleotide comprising SEQ ID NO 21 under conditions effective for amplifying an expressed product. SEQ ID NO 21 is a contig sequence and is not a full length cDNA, thus primers specific for a polynucleotide comprising SEQ ID NO 21 encompasses sequences other than sequences that would hybridize to SEQ ID NO 21, which have not been taught in the specification.

Level of Predictability and Unpredictability in the Art

The art does not teach detecting overexpression of SEQ ID NO 21 under moderately stringent conditions. The specification does teach that SEQ ID NO 21 has homology to LI cadherin. A sequence search revealed that SEQ ID NO 21 is identical to LI cadherin except for two mismatches at nucleotides 1 and 3 as well as an insertion of an "n" at position 257 of SEQ ID NO 21. The post filing date art, however, teaches (Grotzinger et al., Gut, July 2001, vol. 49, pp 73-81) that LI-cadherin is expressed in the small and large bowel of healthy individuals but is not expressed in the oesophagus and stomach, and that 12 (from 10 patients) of 77 (from 30 patients) gastric biopsies from patients with intestinal metaplasia stained positive for LI-cadherin. Thus, Grotzinger teaches that while expression of LI-cadherin appears to be associated with

gastric intestinal metaplasia, Grotzinger also teaches that LI-cadherin is expressed in the large intestine of healthy individuals.

Quantity of Experimentation Necessary

Therefore, based on the lack of guidance from the specification, and the teachings of the art, it would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. Firstly, the specification provides no guidance as to whether the presence of colon cancer can be detected in a patient by detecting an overexpression of SEQ ID NO 21, sequences comprising SEQ ID NO 21, mutants, homologs, or variants of SEQ ID NO 21 in any biological sample. The recitation of biological samples encompasses blood, sputum, saliva, urine, and tissues from any source however the specification has not taught that an overexpression of SEQ ID NO 21, sequences comprising SEQ ID NO 21, mutants, homologs, or variants of SEQ ID NO 21 can be detected in any other tissues except for normal colon or colon tumor tissue. For example, neither the specification nor the art provide evidence that mRNA expression, let alone elevated mRNA expression of SEQ ID NO 21 can be detected in a blood sample from a patient. Secondly, the specification teaches that SEQ ID NO 21 showed two or more fold over overexpression in the colon tumor group as compared to the normal tissue group (p. 52), however the normal tissue group encompasses a large number of different tissues, and the result of this micro array study could be due to the fact that the expression of SEQ ID NO 21 is colon tissue specific, and not colon tumor tissue specific. It is noted that SEQ ID NO 21 shows strong homology (2 mismatches and an insertion for over 346 nucleotides of SEQ ID NO

21 relative to a portion of LI cadherin) to a portion of LI-cadherin which is known in the art to be expressed in the large intestine but not the stomach or esophagus of healthy individuals (see Grotzinger). Thirdly, the specification further teaches that overexpression of SEQ ID NO 21 was found in about half of colon tumors and that 'low level overexpression' was found in 3/6 normal colon tissues, however, the specification does not teach the level of expression in the other 3 normal colon tissues. Further, given that the sample size for normal colon tissue taught by the specification is small (6) and that the specification only teaches a "relative" level of expression for 3 of the 6 samples, and further that the specification does not teach whether the difference between overexpression and "low level overexpression" was statistically significant, or how one of skill in the art would distinguish overexpression from 'low level overexpression', undue experimentation would be required of the skilled artisan to determine whether a predictable correlation exists between elevated expression of SEQ ID NO 21 mRNA in colon tumor tissue and colon cancer.

Further, a correlation between an increase in expression of SEQ ID NO 21 or mutants, homologs, or variants of SEQ ID NO 21 and progression of colon cancer is clearly unpredictable in light of the lack of guidance from the specification and the art. It is unclear whether expression of SEQ ID NO 21 increases with progression or decreases with remission of colon cancer. Without evidence as to the correlation between expression of SEQ ID NO 21, or mutants, variants, or homologs of SEQ ID NO 21, the skilled artisan would be required to practice undo experimentation to determine whether a correlation exists between an increase in

elevated expression of SEQ ID NO 21 or mutants, homologs, or variants of SEQ ID NO 21 and progression of colon cancer in a patient. Consequently since the art does not show a correlation between an increase in elevated SEQ ID NO 21 expression and the progression of colon cancer and since the specification offers no guidance as to such a correlation, and because the level of unpredictability of the correlation between elevated SEQ ID NO 21 expression and presence of colon cancer, let alone progression of colon cancer, is high, undo experimentation would be required by the skilled artisan to make and use the claimed invention.

Response to Arguments

The response traverses the rejection. The response agrees with the examiner's position that, based on the evidence presented in the specification, SEQ ID NO 21 appears to be a colon tissue specific transcript and not a colon tumor specific transcript. The response then asserts that the skilled artisan would recognize that the difference in expression between colon tumor tissue and normal colon is not relevant for the instant invention. The response further asserts at p 7 that a correlation between an increase in expression of SEQ ID NO 21 per se and progression of colon cancer is not necessary. These arguments has been thoroughly reviewed but were found unpersuasive. Firstly, as the claims are presently written, they encompass a method which detects colon cancer by detecting overexpression (which can be an increase in amount as in claims 79, 82, 86 and 87) or underexpression of SEQ ID NO 21 (claim 86 does not distinguish between the two, it just compares two different expressed products to a predetermined cutoff value). It is further noted, that none of these claims indicate a specific biological sample, and

that therefore, the claims encompass comparing colon tumor and normal tissue, which also encompasses normal colon tissue), which the specification contemplates (see for example p. 14, last para; and p. 47, 2nd full para) but does not demonstrate with regard to SEQ ID NO 21. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art.

The response further asserts that with regard to colon cancer and detection of overexpression of SEQ ID NO 21 in blood, the specification teaches that no significant levels of expression of SEQ ID NO 21 was detected in resting and activated PBMC (found in blood) or any other normal tissue tested. This argument has been thoroughly reviewed but was found unpersuasive as the specification teaches that SEQ ID NO 21 was expressed (mRNA) in normal colon tissue.

The response traverses that although the examiner alleges that the specification does not provide evidence that the protein of SEQ ID NO 21 is elevated at least two fold in colon tumor tissue as compared to normal tissue, one of skill in the art would recognize that expression of mRNA is a first and necessary step in the expression of a polypeptide and that there is a

reasonable expectation of correlation between the expression of mRNA and protein. This argument has been thoroughly reviewed but was not found persuasive because the specification has not demonstrated that SEQ ID NO 21 is overexpressed at least two fold in colon tumor tissue as compared to normal tissue, encompasses normal colon tissue. Further, the declaration of Gary Fanger, which detects C888P, also does not demonstrate such. Further, it is noted that the declaration also teaches that C888P positive membrane staining was detected in appendix and gallbladder, and that marginal staining was detected in normal salivary gland and stomach.

Further, the declarations have been thoroughly reviewed but were not found persuasive for the following reasons. Firstly, the nexus between the experiments conducted in the declaration of Gary Fanger, Ph.D., and the teachings in the specification are unclear. The declaration asserts that the full length polynucleotide sequence comprising SEQ ID NO 21 was analyzed by immunohistochemistry (IHC). However, it is not clear whether the sequence of L1-cadherin was used, as taught by Genbank Accession number NM_004063, or whether sequence of L1-cadherin as it relates to SEQ ID NO 21, that is without the mismatches and insertion present in L1-cadherin relative to SEQ ID NO 21. It is noted that the specification does not teach immunohistochemistry experiments with L1-cadherin. Further, it is noted that the specification does not teach the nucleotide sequence which is "the full length sequence comprising SEQ ID NO 21". The declaration asserts that IHC staining indicated that expression of C888P is plasma membrane associated in both colon cancer and normal colon tissue, but that the staining patterns between normal colon and colon tumor tissue are distinct and that therefore, antibodies can be

used in IHC to differentiate normal colon from colon cancer tissue. This argument has been thoroughly reviewed but was found unpersuasive as there is no nexus between the experiments conducted in the declaration and the claims pending. The instant claims are directed to detecting colon cancer or progression of colon cancer by detecting an increase in amount (which encompasses an increase in expression) of nucleic acid hybridizable to SEQ ID NO 21, or to SEQ ID NO 21 itself in any biological sample, whereas the experiments in the declaration are directed to detecting a difference in antibody staining in specific cell populations of normal colon and colon cancer tissue. At the time of filing, the specification did not teach that IHC staining C888P patterns in colon tissue and colon tumor tissue were distinct. As stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocol is not disclosed in the specification indicates that the specification does not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention. Therefore, while the declaration asserts that C888P antibody staining patterns are different in colon tissue and colon tumor tissue, such teaching does not necessarily indicate that an increase in *amount* of mRNA levels corresponding to SEQ ID NO 21, or variants, mutants, or homologs of SEQ ID NO 21 would indicate the presence of colon cancer or the progression of colon cancer.

The declaration of Susan Harlocker, Ph.D., has also been thoroughly reviewed. In such, it is asserted that the differences between SEQ ID NO 21 and L1-cadherin appear to be due to sequencing errors and that SEQ ID NO 21 is a fragment of L1-cadherin. If such is the case, the assertion of specificity of SEQ ID NO 21 to colon tissue is not supported by the art, which teaches that L1-cadherin is a marker for gastric metaplasia and neoplasia (see Grotzinger et al). Grotzinger et al teach immunohistochemical analysis of L1-cadherin with antibodies in patients some of which with intestinal metaplasia, and that some patients showed positive staining for L1-cadherin in gastric glands (see 76). Grotzinger further teaches that patients with gastric carcinoma exhibited intense immune staining for L1-cadherin, and that such staining was able to differentiate tumor cells and mesenchymal tissue and inflammatory infiltrates.

The response also traverses that the an artisan skilled in the diagnostic arts would have no difficulty identifying a suitable negative or normal control value, that is, a predetermined cut of value. The response that a predetermined cut off value is simply not needed, when the skilled artisan would fully appreciate the routine nature of identifying a suitable valuc for the assay being employed. This argument has been thoroughly reviewed but was found unpersuasive. As stated in previous office actions, the art teaches that LI-cadherin was expressed in the large intestine of *healthy* individuals (see Grotzinger). This evidence coupled with the vague description of a difference in expression between colon tumor and normal tissue, which encompassed normal colon tissue, ('overexpression' vs 'low level overexpression') taught by the specification demonstrates the unpredictability of determining the presence of colon cancer in a

patient based on the expression of SEQ ID NO 21 relative to a predetermined cut off value. Since, the specification does not teach what level of expression of SEQ ID NO 21, or mutants, homologs, or variants of SEQ ID NO 21 constitutes an acceptable predetermined cut off value, the claims provide that the skilled artisan must determine that value. The Court in *Genetech Inc. V Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". Further, should the skilled artisan use the definition of a "colon tumor protein" on page 14 of the specification to determine this predetermined cut off value, the specification provides insufficient guidance for the definition as the specification teaches that SEQ ID NO 21, not the protein expressed by SEQ ID NO 21, showed 'overexpression' in half of colon tumor tissue tested versus 'low level overexpression' in 3/6 normal colon tissue. Further, the specification does not teach whether 'overexpression' constitutes two or more fold overexpression relative to the 'low level overexpression' detected for 3/6 normal colon tissue samples.

The response asserts the removal of the recitation of sequences having 90% identity to SEQ ID NO 21 obviates the grounds for rejection with regard to the specification providing no teaching of mutants, homologs, or variants of SEQ ID NO 21. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, it is noted that claim 85, still recites 90% identity to SEQ ID NO 21. Secondly, the broad recitation of "moderately stringent conditions" in claims 79 and 82, the recitation of primers specific for a sequence "comprising

SEQ ID NO 21" (which encompasses sequences not disclosed by SEQ ID NO 21) in newly added claims 86 and 87, still encompasses mutants, variants, and homologs of SEQ ID NO 21.

For these reasons, and reasons made of record in previous office actions, the rejection is maintained.

Indefinite

7. Claim 86 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 86 lacks antecedent basis for the recitation of "said product" in step c (second iteration) because it is unclear if the product being compared is the expressed produce amplified in step a or step b. Claim 86 is also indefinite as it recites two different step c, and thus it is unclear if they are practiced together as one step, or if the second disclosure of step c in the claim is meant to be an additional step.

Claim Objections

8. Newly added claim 87 is objected to because it contains a (.) in the second to last line of step d. Appropriate correction is Required.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634

Jehanne Souaya
11/29/02

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600